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Therapeutic Review
β_2-Agonist Combination Products

Overview/Summary

The combination respiratory β_2-adrenergic agonist class consists of two products (Combivent® and DuoNeb®) that contain a combination of the bronchodilators albuterol and ipratropium. These combination products are Food and Drug Administration (FDA)-approved for the treatment of chronic obstructive pulmonary disease (COPD).[1-4] Although the use of albuterol/ipratropium for the treatment of asthma has not been approved by the FDA, this combination product has been utilized off label for the treatment of severe-persistent asthma in patients who fail recommended asthma therapy.[3-4] Albuterol is a selective β_2-agonist that relaxes the smooth muscles in the airways, resulting in bronchodilation. Ipratropium is an anticholinergic that blocks the effects of acetylcholine, which results in bronchodilation.[1-4] Combivent® is available as metered dose inhaler (MDI) and DuoNeb® is available as a nebulization solution. DuoNeb® is the only one of these two products available generically.[1-4]

As a result of the Clean Air Act and the Montreal Protocol on Substances that Deplete the Ozone Layer, the FDA made the decision to end production, marketing, and sale of all albuterol MDIs containing chlorofluorocarbons (CFCs) as their propellant by December 31, 2008. Currently all CFC MDIs are being replaced by MDIs that utilize hydrofluoroalkanes (HFAs) as their propellants. This ruling does not affect Combivent® (albuterol/ipratropium) as it has been designated as an essential-use product by the United States Department of Health and Human Services and FDA. HFA MDIs provide the same level of safety and efficacy as CFC MDIs, but without harming the ozone layer.[6]

According to the National Heart, Lung, and Blood Institute (NHLBI)/National Asthma Education and Prevention Program (NAEPP) and the Global Initiative for Asthma (GINA), inhaled corticosteroids (ICSs) are the most effective long-term control medications used for the treatment of asthma for patients of all ages.[7,8] Alternative long-term control medications include leukotriene modifiers, mast-cell stabilizers, and methylxanthines, however these agents are considered less effective as monotherapy compared to ICSs. Long-acting β_2-agonists (LABAs) should not be used as monotherapy for the management of asthma; however, they are considered the most effective adjunctive therapy in patients who are not adequately controlled with an ICS alone. Leukotriene modifiers, mast-cell stabilizers, and methylxanthines may also be used as adjunctive therapies but are less effective than the LABAs. Chronic administration of systemic corticosteroids is reserved for severe, difficult-to-control asthma patients and the use of immunomodulators is only indicated in asthma patients with severe disease and allergies.

Current clinical guidelines also state that short-acting β_2-agonists (SABAs) are the medication of choice for the relief of bronchospasm during acute exacerbations of asthma.[7,8] Anticholinergics may also be used for the treatment of acute exacerbations but are considered less effective than SABAs.[1] The addition of a systemic corticosteroid may be required if patients do not respond immediately to treatment with a SABA or if the exacerbation is severe.[2] According to the NHLBI/NAEPP, the use of LABAs to treat acute symptoms or exacerbations of asthma is not currently recommended.[7]

According to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines, agents used to manage stable chronic obstructive pulmonary disease (COPD) include inhaled bronchodilators and corticosteroids.[9] The choice between bronchodilators, which are central to COPD symptom management, depends on patient response, the incidence of adverse events, and availability. Bronchodilators, which include long- and short-acting β_2-agonists, anticholinergics, and methylxanthines, should be administered as needed or on a scheduled basis to relieve intermittent or worsening symptoms or to prevent or reduce persistent symptoms. Long-acting bronchodilators are more effective and convenient than short-acting

bronchodilators however short-acting bronchodilators should be considered initial empiric therapy.[9,10] According to the National Institute for Clinical Excellence, long-acting bronchodilators should be used to control symptoms of COPD in patients who continue to experience problems despite the use of short-acting bronchodilators.[10] Also, a combination of bronchodilators from different pharmacologic classes may increase the efficacy of the treatment regimen. The addition of an inhaled corticosteroid to a treatment regimen reduces exacerbations and improves lung function.[9] Long-term treatment with oral corticosteroids is not recommended for the management of stable COPD.

Current GOLD guidelines also recommend the use of bronchodilators and corticosteroids for the management of acute COPD exacerbations.[9] An increase in the dose and/or frequency of short-acting bronchodilators as well as the addition of an anticholinergic until symptoms improve is recommended. For patients with a baseline Forced Expiratory Volume in one second (FEV_1) <50% predicted, the addition of oral corticosteroids is recommended for the management of acute exacerbations. The use of antibiotics in COPD is only recommended for the treatment of infectious exacerbations.

Medications

Table 1. Medications Included Within Class Review

Generic Name (Trade name)	Medication Class	Generic Availability
Albuterol/ipratropium (Combivent®, DuoNeb®*)	Inhaled β_2-adrenegic agonists/anticholinergic	✔ (DuoNeb®)

*Individual components are available generically.

Indications

Table 2. Food and Drug Administration Approved Indication[1-4]

Indication*	Albuterol/Ipratropium
Emphysema	✔
Chronic Bronchitis	✔

* Emphysema and chronic bronchitis are synonymous with the term chronic obstructive pulmonary disease (COPD).

Currently both agents are indicated for the treatment of bronchospasm associated with chronic obstructive pulmonary disease (COPD) in patients requiring more than one bronchodilator. However, an off-labeled indication for the combination of albuterol/ipratropium is for the treatment of severe-asthma.[1-4]

Pharmacokinetics

Table 3. Pharmacokinetics[1-4]

Generic Name	Onset (hours)	Duration (hours)	Renal Excretion (%)	Active Metabolites	Serum Half-Life (hours)
Albuterol/ ipratropium	0.25-1	3-6	27; predominantly albuterol	Yes (albuterol) No (ipratropium)	4 (albuterol meter dose inhaler) 6.7 (albuterol solution) 2 (ipratropium meter dose inhaler and solution)

Clinical Trials

For the treatment of chronic obstructive pulmonary disease (COPD), national and international treatment guidelines state that no medication has been shown to modify the long-term decline in the lung function that is associated with the disease. Guidelines do recommend that treatment should be focused on reducing the symptoms and complications of the disease.[19.20] All agents used in the treatment of COPD (i.e., inhaled corticosteroids, inhaled anticholinergics, β_2-agonists, and methylxanthines) can improve

symptoms, exacerbations, and disease complications.[7-10] National and international treatment guidelines recognize the efficacy of these agents for their respective indications and note that all available formulation are equally efficacious; however they give giving no preferential status to one agent in a specific class over another in the same class.[9-10]

Clinical trials conducted in the 1990's have demonstrated the safety and efficacy of albuterol and ipratropium either as monotherapy or in combination, in providing symptomatic relief of COPD exacerbations.[11-14] A recent study, conducted by Tashkin et al, evaluated COPD patients receiving albuterol/ipratropium via metered dose inhaler (MDI), via nebulization or via nebulizer in the morning and MDI at noon and in the evening.[16] The primary endpoint evaluated was the change in quality of life, measured by the St. George's Respiratory Questionnaire, at weeks 6 and 12. At week 6, the combination nebulization and MDI group was the only treatment group that demonstrated a statistically significant difference compared to baseline (-5.2±2.33; P<0.0196). At week 12, no treatment group demonstrated a statistically significant difference. There were no statistically significant differences between the three treatments.[16]

Table 4. Clinical Trials

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Ikeda et al[11] Ipratropium 40 µg via MDI vs ipratropium 80 µg via MDI vs albuterol 200 µg via MDI and ipratropium 40 µg via MDI (administered as separate products) vs albuterol 400 µg via MDI and ipratropium 80 µg via MDI (administered as separate products) vs placebo	DB, PC, RCT, XO Adult male patients with stable COPD with a history of greater than 20 pack-years of cigarette smoking, and FEV_1 <60% and a FEV_1 /FVC<0.7, and a chest radiographic findings compatible with pulmonary emphysema	N=26 5 separate visits over a period of 1 month	Primary: Change from baseline in FEV_1, FVC as well the difference in adverse reactions reported Secondary: Not reported	Primary: All treatment groups resulted in a significant improvement in FEV_1 and FVC when compared with placebo at all time points evaluated *(P*<0.01). Compared to all other regimens at every time point evaluated, 80 µg of ipratropium and 400 µg of albuterol showed significantly greater improvements in FEV_1 (*P*<0.05, *P*<0.01). The lower dose combination was significantly different in FVC response from the low-dose monotherapy (*P*<0.01), but not high-dose monotherapy. No significant differences were found in terms of the safety of the medications, including pulse rate, blood pressure, and averse effects (no *P* value reported). Secondary: Not reported
Bone et al[12] Albuterol 100 µg QID via MDI vs ipratropium 21 µg QID via	DB, MC, PG, PRO, RCT Patient's ≥40 years of age diagnosed with COPD with stable disease, relative stable, moderately	N=534 85 days	Primary: Peak change from baseline in FEV_1, response AUC, symptom score, and safety	Primary: Compared to the individual components, the mean peak response in FEV_1 was significantly greater in the combination treatment group (*P*<0.001 to *P*=0.015). There was no difference in symptom score between the groups (no *P* value reported).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
MDI vs albuterol/ipratropium 100/21 µg QID via MDI (administered as a combination product)	severe airway obstruction with an FEV_1 ≤65% and FEV_1/FVC ratio ≤0.70, and a smoking history >10 pack-years, using at least two prescribed therapeutic agents for COPD control		Secondary: Not reported	Compared with either agent alone, the overall FVC response was significantly greater in the combination group (*P*<0.01 to *P*=0.04). There were no significant differences between any of the treatment groups in terms of adverse effects or safety (no *P* value reported). Secondary: Not reported
Dorinsky et al[13] Albuterol 180 µg QID via MDI vs ipratropium 36 µg QID via MDI vs equivalent dose of albuterol/ipratropium via MDI (administered as a combination product)	DB, MC, PG, RETRO, RCT Patients ≥40 years old diagnosed with COPD, >10 pack year smoking history, regularly using at least two bronchodilators for symptom control during 3 months prior to the trials, FEV_1 ≤65% predicted value, FEV_1/FVC ratio ≤0.70	N=1,067 85 days	Primary: FEV_1 and FVC values before and after administration of the study medications (bronchodilator response defined as increase in FEV_1 of 12% and 15% from baseline) Secondary: Not reported	Primary: The percentage of patients demonstrating a 15% increase in FEV_1 at 15 and 30 minutes after medication administration was significantly higher in the albuterol/ipratropium group compared to the individual treatment groups on all test days, and significantly higher than the individual treatment groups after 60 and 120 minutes on test day 1 and 2 (of 4) (*P*<0.05). Overall decline in percentage of patients demonstrating a 15% increase in FEV_1 in all groups was small and ranged from 2%-8% (no *P* value reported). Significantly greater percentage of patients demonstrated a 12% or 15% increase in FEV_1 on 3 or more test days in albuterol/ipratropium group compared to the individual treatment groups (*P*<0.05). Secondary: Not reported
Friedman et al[14] Albuterol 180 µg QID via MDI vs ipratropium 36 µg QID via	DB, MC, PG, RETRO, RCT Patients ≥40 years old diagnosed with COPD, >10 pack year smoking history, regularly using at	N=1,067 85 days	Primary: Peak change in FEV_1 and the FEV_1 AUC from time 0-4 hours, total health care expenditures, and cost effectiveness ratios	Primary: Statistically significant improvement in FEV_1 in albuterol/ipratropium group compared to other treatment groups on all test days (*P*<0.01). Significantly higher FEV_1 AUC_{0-4} in albuterol/ipratropium group compared to other treatment groups on all test days (*P*≤0.008). Total cost of treating patients in the ipratropium monotherapy group and

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
MDI vs equivalent dose of albuterol/ipratropium via MDI (administered as a combination product)	least two bronchodilators for symptom control during the 3 months prior to the trials, $FEV_1 \leq 65\%$ predicted value, $FEV_1 \leq 70\%$ of FVC		Secondary: Not reported	the albuterol/ipratropium group was significantly less than the albuterol monotherapy group (no *P* value reported). No statistical difference between total costs in the ipratropium group and the albuterol/ipratropium group (no *P* value reported). Significantly greater cost effectiveness in ipratropium monotherapy and albuterol/ipratropium combination groups compared to albuterol monotherapy group ($P<0.05$). Secondary: Not reported
Tashkin et al[15] Albuterol/ipratropium solution for nebulization QID (administered as a combination product) vs albuterol/ipratropium 2 inhalations QID via MDI (administered as a combination product) vs albuterol/ipratropium solution for nebulization administered in the morning and albuterol/ ipratropium MDI administered in the afternoon and evening (both administered as a	MC, PG, RCT Men and women ≥50 years old who met the American Thoracic Society/ European Respiratory Society definition of COPD, had a history of >10 pack-years of cigarette smoking, an FEV_1 30%-65% of the predicted value, and a post bronchodilator FEV_1/FVC ratio ≤0.70	N=140 N=37 (nebulization) N=43 (MDI) N=46 (nebulization and MDI) 12-weeks	Primary: Quality of life (St. George's Respiratory Questionnaire, completed at baseline, 6 weeks, and 12 weeks) Secondary: Patient Symptom Score, home morning and nighttime daily peak flow before dosing with the study medication and pre- and post-dose FEV_1 in the clinic, safety measures (vital signs, changes in physical findings, and investigator reported disease	Primary: Baseline quality of life total score was similar in all three-study groups. After 6 weeks of treatment, the change from baseline in the Total Quality of Life score was clinically (exceeding the 4-unit threshold) and statistically significant for the concomitant treat group (-5.2±2.33; $P<0.0196$). Patients in the nebulizer-only treatment group approached clinically significant improvements (-3.7±2.21; *P* value not reported). Differences between the treatment groups at week 6 were not statistically significant. Statistically significant improvement was seen in Symptoms sub-score at week 6 for patients using a nebulizer-only or concomitant treatment ($P=0.019$ and $P<0.004$, respectively). Only the concomitant therapy group achieved a clinically significant improvement from baseline at week 6 in the Impacts sub-score (-5.1± 3.00), however results were not statistically significant (*P* value not reported). At week 12 only the concomitant therapy group approached a clinically significant improvement in Total score (-3.5±2.64). Both the concomitant and nebulizer-only treatment groups demonstrated an improvement in the Symptoms sub-score (-6.1±3.00; $P=0.0186$, -

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
combination product)			exacerbations)	4.0±3.83; *P* value not reported, respectively). None of the treatment groups reached a clinically significant improvement in the Impacts sub-score. Changes between the treatment groups in the endpoints measured were not statistically significant Secondary: Changes in pre- and post-bronchodilator FEV_1 with the treatment groups were not statistically significant at week 6 or at week 12; only the MDI inhaler treatment group demonstrated a statistically significant change from baseline at week 6 (*P*=0.0060). Mean Patients Symptom Scores were similar among the treatment groups at baseline. All three-treatment groups demonstrated an improvement in Patient Symptom Scores from baseline to week 6 and week 12. • Concomitant group ○ Baseline 5.60±0.52 ○ Week 6: 3.90±0.51; *P*=0.0312 ○ Week 12: 4.30±0.57; *P*=0.0490 • Nebulizer-only group ○ Baseline 5.80±0.60 ○ Week 6: 4.60±0.57; *P*=0.0539 ○ Week 12: 4.80±0.64; *P*=0.0461 • Inhaler-only group ○ Baseline 5.80±0.53 ○ Week 6: 4.50±0.50; *P* value not reported ○ Week 12: 4.30±0.56; *P* value not reported The differences in adverse events were not discussed.

Drug regimen abbreviations: QID=four times daily
Study abbreviations: DB=double-blind, MC=multicenter, PC=placebo-controlled, PG=parallel-group, PRO=prospective, RCT=randomized controlled trial, RETRO=retrospective, SD=single dose, XO=crossover
Miscellaneous abbreviations: COPD=chronic obstructive pulmonary disease, FEV_1=forced expiratory volume in 1 second, FVC=forced vital capacity, MDI=metered dose inhaler

Special Populations

Table 5. Special Populations[1-4]

Generic Name	Population and Precaution				
	Elderly/ Children	Renal Dysfunction	Hepatic Dysfunction	Pregnancy Category	Excreted in Breast Milk Other
Albuterol/ ipratropium	No overall differences in safety or efficacy were observed between elderly and younger patients. Safety and efficacy has not been established in children.	Unknown; not studied in patients with renal dysfunction.	Unknown; not studied in patients with hepatic dysfunction.	C	Unknown; importance of drug administration to mother should be determined.

Adverse Drug Events

Common adverse reactions reported with the albuterol/ipratropium are summarized in Table 6. The most common adverse events reported were upper respiratory tract infection, pharyngitis, headache and dyspnea. The table below is indicative only of those with the highest reported frequency or those listed as most common.

Table 6. Adverse Drug Events (%)[1-4]

Adverse Events	Albuterol/Ipratropium (solution for inhalation)	Albuterol/Ipratropium (metered dose inhaler)
Cardiovascular		
Angina	-	<2
Arrhythmia	-	<2
Chest pain	2.6	0.3
Elevated heart rate	✔	-
Hypertension	-	<2
Hypotension	-	✔
Palpitations	-	<2
Tachycardia	-	<2
Central Nervous System		
Central nervous system stimulation	-	✔
Coordination difficulty	-	✔
Dizziness	-	<2
Drowsiness	✔	✔
Fatigue	-	<2
Flushing	✔	✔
Headache	-	5.6
Insomnia	-	<2
Nervousness	-	<2
Tremor	-	<2
Weakness	-	✔
Dermatological		
Angioedema	-	<2

Adverse Events	Albuterol/Ipratropium (solution for inhalation)	Albuterol/Ipratropium (metered dose inhaler)
Pruritus	✔	-
Skin rash	✔	-
Urticaria	✔	<2
Gastrointestinal		
Constipation	✔	✔
Diarrhea	1.8	<2
Dry mouth	-	<2
Dyspepsia	1.3	<2
Gastrointestinal distress	-	✔
Heartburn	-	✔
Nausea	1.4	2.0
Sore throat	✔	-
Taste perversion	-	<2
Vomiting	-	<2
Genitourinary		
Urinary difficulty	-	✔
Urinary tract infection	1.6	<2
Musculoskeletal		
Arthralgia	-	<2
Back pain	✔	-
Cramps leg	1.4	-
Pain	1.3	2.5
Respiratory		
Bronchitis	1.7	12.3
Bronchospasm	✔	0.3
Chronic obstructive pulmonary disease exacerbation	✔	✔
Coughing	-	4.2
Drying of secretions	-	✔
Dysphonia	-	<2
Dyspnea	-	4.5
Increased sputum	-	<2
Influenza	-	1.4
Irritation from aerosol	-	✔
Laryngospasm	-	<2
Lung disease	6.4	-
Nasal congestion	-	✔
Pharyngitis	4.4	2.2
Pneumonia	1.3	1.4
Respiratory disorder	-	2.5
Rhinitis	-	1.1
Sinusitis	✔	2.3
Upper respiratory tract infection	-	10.9
Voice alterations	✔	-
Wheezing	✔	✔
Other		
Acute eye pain	✔	✔
Alopecia	-	✔
Anaphylactic reaction	-	<2
Blurred vision	✔	✔

Adverse Events	Albuterol/Ipratropium (solution for inhalation)	Albuterol/Ipratropium (metered dose inhaler)
Edema	-	<2
Worsening glaucoma	✔	✔

Contraindications / Precautions

β_2-adrenergic agonist (albuterol): In some patients, the use of β_2-agonists have been associated with electrocardiogram changes such as flattening of the T-wave, prolongation of the QTc interval, and ST segment depression. β_2-agonists can produce clinically significant cardiovascular effects in some patients (i.e., increase pulse rate and blood pressure). In some patients, the use of β_2-agonists can produce paradoxical bronchospasm, which may be life threatening. Immediate discontinuation of the medication should occur if paradoxical bronchospasm is suspected.

Anticholinergics (ipratropium): Ipratropium is contraindicated in patients with a hypersensitivity to ipratropium and/or atropine and its derivatives. Ipratropium inhalation is for the maintenance treatment of bronchospasm associated with chronic obstructive pulmonary disease and is not indicated for the initial treatment of acute episodes of bronchospasm where rescue therapy is required for rapid response (i.e., albuterol). In some patients, the use of albuterol and ipratropium may cause paradoxical bronchospasm. Immediate discontinuation of the medication should occur if paradoxical bronchospasm is suspected.

Drug Interactions

Significant drug interactions with the combination β_2-adrenergic agonists are summarized in Table 7.

Table 7. Drug Interactions[1-4]

Generic Name	Interacting Medication or Disease	Potential Result
β_2-adrenergic agonists (all)	Diuretics (i.e., loop diuretics, thiazide diuretics)	Electrocardiogram changes or hypokalemia may potentially be worsened with the addition of a β_2-agonist, particularly when the recommended dose is exceeded.
β_2-adrenergic agonists (all)	Monoamine oxidase inhibitors	Monoamine oxidase is an enzyme that metabolizes catecholamines. When given with an indirect acting sympathomimetic, hypertensive crisis may occur.
β_2-adrenergic agonists (all)	Nonselective β-blocking agents	β-blockers inhibit the therapeutic effects of β_2 agonists and may produce bronchospasm in patients with asthma and chronic obstructive pulmonary disease.
β_2-adrenergic agonists (all)	Tricyclic antidepressants	Tricyclic antidepressant may potentiate the cardiovascular effects of β-adrenergic agonists.
Ipratropium	Anticholinergic agents	Due to a potential for an additive interaction/effect, caution is advised when using ipratropium concomitantly with other anticholinergic-containing medications.

Dosage and Administration

Table 8. Dosing and Administration[1-4]

Generic Name	Adult Dose	Pediatric Dose	Availability
Albuterol/ ipratropium	Nebulization solution: 1 vial (albuterol/ ipratropium 2.5/0.5 mg) 4 times daily; maximum, 6 vials daily MDI: 2 inhalations (albuterol/ ipratropium 120/21 µg) 4 times a daily; maximum, 12 inhalations daily	Safety and effectiveness in children have not been established.	MDI (200 inhalations): 120/21 µg* Nebulization solution (3 mL vials): 3.0/0.5 mg†

MDI=meter dose inhaler.
* Delivering 103 µg of albuterol (90 µg albuterol base) and 18 µg of ipratropium.
†Delivering 2.5 mg albuterol base.

Clinical Guidelines

Table 9. Clinical Guidelines

Clinical Guidelines	Recommendations
The National Heart, Lung, and Blood Institute (NHLBI)/ National Asthma Education and Prevention Program (NAEPP): **Guidelines for the Diagnosis and Management of Asthma (2007)**[7]	Diagnosis • To establish a diagnosis of asthma, a clinician must determine the presence of episodic symptoms or airflow obstruction, partially reversible airflow obstruction, and alternate diagnoses must be excluded. • The recommended methods to establish a diagnosis are a detailed medical history, physical exam focusing on the upper respiratory tract, spirometry to demonstrate obstruction and assess reversibility, and additional studies to exclude alternate diagnoses. • A diagnosis of asthma should be considered if any of the following indicators are present: wheezing, history of cough, recurrent wheeze, difficulty breathing or chest tightness, symptoms that occur or worsen with exercise or viral infections, and symptoms that occur or worsen at night. • Spirometry is needed to establish a diagnosis of asthma. • Additional studies such as additional pulmonary function tests, bronchoprovocation, chest x-ray, allergy testing, and biomarkers of inflammation may be useful when considering alternative diagnoses. Treatment • Pharmacologic therapy is used to prevent and control asthma symptoms, improve quality of life, reduce the frequency and severity of asthma exacerbations, and reverse airflow obstruction. • For initiating treatment, asthma severity should be classified, and the initial treatment should correspond to the appropriate severity category. • Long-term control medications such as inhaled corticosteroids (ICSs), long-acting bronchodilators, leukotriene modifiers, cromolyn, theophylline, and immunomodulators should be taken daily on a long-term basis to achieve and maintain control of persistent asthma. • Quick-relief medications are used to provide prompt relief of bronchoconstriction and accompanying acute symptoms such as cough, chest tightness, and wheezing. • Quick relief medications include short-acting β_2-agonists (SABAs), anticholinergics, and systemic corticosteroids. Long-term Control Medications • ICSs are the most potent and consistently effective long-term control medication for asthma in patients of all ages. • Short courses of oral systemic corticosteroids may be used to gain prompt control when initiating long-term therapy and chronic administration is only used for the most severe, difficult-to-control asthma. • When patients ≥12 years of age require more than low-dose ICSs, the addition of a long-acting β_2-agonist (LABA) is recommended. Alternative, but not preferred, adjunctive therapies include leukotriene receptor antagonists (LTRAs), theophylline, or in adults, zileuton. • Mast cell stabilizers (cromolyn and nedocromil) are used as alternatives for the treatment of mild persistent asthma. They can also be used as preventative treatment prior to exercise or unavoidable exposure to known allergens. • Omalizumab, an immunomodulator, is used as adjunctive therapy in patient's ≥12 years old who have allergies and severe persistent asthma that is not adequately controlled with the combination of high-dose ICS and

<table>
<tr><th>Clinical Guidelines</th><th>Recommendations</th></tr>
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LABA therapy.
• LTRAs (montelukast and zafirlukast) are alternative therapies for the treatment of mild persistent asthma.
• LABAs (salmeterol and formoterol) are not to be used as monotherapy for long-term control of persistent asthma.
• LABAs should continue to be considered for adjunctive therapy in patient's ≥5 years of age who have asthma that require more than low-dose ICSs. For patients inadequately controlled on low-dose ICSs, the option to increase the ICS should be given equal weight to the addition of a LABA.
• Methylxanthines, such as sustained-release theophylline, may be used as an alternative treatment for mild persistent asthma.
• Tiotropium bromide is a long-acting inhaled anticholinergic indicated once-daily for chronic obstructive pulmonary disease and has not been studied in the long-term management of asthma.

Quick-relief Medications
• SABAs are the therapy of choice for relief of acute symptoms and prevention of exercise-induced bronchospasm.
• There is inconsistent data regarding the superior efficacy of levalbuterol over albuterol. Some studies suggest an improved efficacy while other studies fail to detect any advantage of levalbuterol.
• Anticholinergics may be used as an alternative bronchodilator for patients who do not tolerate SABAs and provide additive benefit to SABAs in moderate-to-severe asthma exacerbations.
• Systemic corticosteroids are used for moderate and severe exacerbations as adjunct to SABAs to speed recovery and prevent recurrence of exacerbations.
• The use of LABAs is not currently recommended to treat acute symptoms or exacerbations of asthma.

Assessment, Treatment, and Monitoring
• A stepwise approach to managing asthma is recommended to gain and maintain control of asthma in both the impairment and risk domains.
• Regularly scheduled, daily, chronic use of a SABA is not recommended. Increased use or SABA use >2 days a week for symptom relief generally indicates inadequate asthma control.
• The stepwise approach for managing asthma is outlined below:
<table>
<tr><th>Inter-mittent Asthma</th><th colspan="5">Persistent Asthma: Daily Medication</th></tr>
<tr><th>Step 1</th><th>Step 2</th><th>Step 3</th><th>Step 4</th><th>Step 5</th><th>Step 6</th></tr>
<tr><td>Preferred
SABA as needed</td><td>Preferred
Low-dose ICS

Alternative
Cromolyn, LTRA, nedocromil, or theophylline</td><td>Preferred
Low-dose ICS+LABA OR medium-dose ICS

Alternative
Low-dose ICS+either a LTRA, theophylline, or zileuton</td><td>Preferred
Medium-dose ICS+LABA

Alternative
Medium-dose ICS+either a LTRA, theophylline, or zileuton</td><td>Preferred
High-dose ICS+LABA AND consider omalizumab for patients who have allergies</td><td>Preferred
High-dose ICS+LABA+ oral steroid AND consider omalizumab for patients who have allergies</td></tr>
</table>

Management of Exacerbations
• Appropriate intensification of therapy by increasing inhaled SABAs and, in
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Clinical Guidelines	Recommendations
	some cases, adding a short course of oral systemic corticosteroids is recommended. Special Populations • For exercise-induced bronchospasm, pretreatment before exercise with either a SABA or LABA is recommended. LTRAs may also attenuate exercise-induced bronchospasm and mast cell stabilizers can be taken shortly before exercise as an alternative treatment for prevention however they are not as effective as SABAs. The addition of cromolyn to a SABA is helpful in some individuals who have exercise induced bronchospasm. • Consideration of the risk for specific complications must be given to patients who have asthma who are undergoing surgery. • Albuterol is the preferred SABA in pregnancy because of an excellent safety profile. • ICSs are the preferred treatment for long-term control medication in pregnancy. Specifically, budesonide is the preferred ICS as more data is available on using budesonide in pregnant women than other ICSs.
Global Initiative for Asthma (GINA): **Global Strategy for Asthma Management and Prevention (2008)**[8]	Diagnosis • A clinical diagnosis of asthma is often prompted by symptoms such as episodic breathlessness, wheezing, cough, and chest tightness. • Measurements of lung function (spirometry or peak expiratory flow) provide an assessment of the severity of airflow limitation, its reversibility, and its variability and provide confirmation of the diagnosis of asthma. Treatment • Education should be an integral part of all interactions between health care professionals and patients, and is relevant to asthma patients of all ages. • Measures to prevent the development of asthma, asthma symptoms, and asthma exacerbations by avoiding or reducing exposure to risk factors should be implemented whenever possible. • Controller medications are administered daily on a long-term basis and include inhaled and systemic glucocorticosteroids, leukotriene modifiers, LABAs in combination with inhaled glucocorticosteroids, sustained-released theophylline, cromones, and anti-immunoglobulin E (IgE). • Reliever medications are administered on an as-needed basis to reverse bronchoconstriction and relieve symptoms and include rapid-acting inhaled β_2-agonists, inhaled anticholinergics, short-acting theophylline, and SABAs. Controller Medications • Inhaled glucocorticosteroids are currently the most effective anti-inflammatory medications for the treatment of persistent asthma for patients of all ages. • Inhaled glucocorticosteroids differ in potency and bioavailability, but few studies have confirmed the clinical relevance of these differences. • To reach clinical control, add-on therapy with another class of controller is preferred over increasing the dose of inhaled glucocorticosteroids. • Leukotriene modifiers are generally less effective than inhaled glucocorticosteroids therefore may be used as an alternative treatment in patients with mild persistent asthma. • Some patients with aspirin-sensitive asthma respond well to leukotriene modifiers. • Leukotriene modifiers used as add-on therapy may reduce the dose of inhaled glucocorticosteroids required by patients with moderate to severe

Clinical Guidelines	Recommendations
	asthma, and may improve asthma control in adult patients whose asthma is not controlled with low or high doses of inhaled glucocorticosteroids. • Several studies have demonstrated that leukotriene modifiers are less effective than LABAs as add-on therapy. • LABAs should not be used as monotherapy in patients with asthma as these medications do not appear to influence asthma airway inflammation. • When a medium dose of an inhaled glucocorticosteroid fails to achieve control, the addition of a LABA is the preferred treatment. • Controlled studies have shown that delivering a LABA and an inhaled glucocorticosteroid in a combination inhaler is as effective as giving each drug separately. Fixed combination inhalers are more convenient, may increase compliance, and ensure that the LABA is always accompanied by a glucocorticosteroid. • Although the guideline indicates that combination inhalers containing formoterol and budesonide may be used for both rescue and maintenance, this use is not approved by the Food and Drug Administration (FDA). • Theophylline as add-on therapy is less effective than LABAs but may provide benefit in patients who do not achieve control on inhaled glucocorticosteroids alone. • Cromolyn and nedocromil are less effective than a low dose of an inhaled glucocorticosteroid. • Oral LABA therapy is used only on rare occasions when additional bronchodilation is needed. • Anti-IgE treatment with omalizumab is limited to patients with elevated serum levels of IgE. • Long-term oral glucocorticosteroid therapy may be required for severely uncontrolled asthma, but is limited by the risk of significant adverse effects. • Other anti-allergic compounds have limited effect in the management of asthma. <u>Reliever Medications</u> • Rapid-acting inhaled β_2-agonists are the medications of choice for the relief of bronchospasm during acute exacerbations and for the pretreatment of exercise-induced bronchoconstriction, in patients of all ages. • Rapid-acting inhaled β_2-agonists should be used only on an as-needed basis at the lowest dose and frequency required. • Although the guidelines states that formoterol, a LABA, is approved for symptom relief because of its rapid onset of action, and that it should only be used for this purpose in patients on regular controller therapy with inhaled glucocorticosteroids, the use of this agent as a rescue inhaler is not approved by the FDA. • Ipratropium bromide, an inhaled anticholinergic, is a less effective reliever medication in asthma than rapid-acting inhaled β_2-agonists. • Short-acting theophylline may be considered for relief of asthma symptoms. • Short-acting oral β_2-agonists (tablets, solution, etc.) are appropriate for use in patients who are unable to use inhaled medication however they are associated with a higher prevalence of adverse effects. • Systemic glucocorticosteroids are important in the treatment of severe acute exacerbations. <u>Assessment, Treatment, and Monitoring</u> • The goal of asthma treatment is to achieve and maintain clinical control.

<table>
<tr><th>Clinical Guidelines</th><th>Recommendations</th></tr>
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To aid in clinical management, a classification of asthma by level of control is recommended: controlled, partly controlled, or uncontrolled.
Treatment should be adjusted in a continuous cycle driven by the patient's asthma control status and treatment should be stepped up until control is achieved. When control is maintained for at least three months, treatment can be stepped down.
Increased use, especially daily use, of reliever medication is a warning of deterioration of asthma control and indicates the need to reassess treatment.
The management approach based on control is outlined below:

<table>
<tr><th>Step 1</th><th>Step 2</th><th>Step 3</th><th>Step 4</th><th>Step 5</th></tr>
<tr><td colspan="5">Asthma education and environmental control</td></tr>
<tr><td colspan="5">As needed rapid-acting β_2-agonist</td></tr>
<tr><td rowspan="6">Controller options</td><td>Select one</td><td colspan="2">Select one</td><td>Add one or more</td><td>Add one or both</td></tr>
<tr><td>Low-dose inhaled glucocorticosteroid</td><td colspan="2">Low-dose inhaled glucocorticosteroid +LABA</td><td>Medium- or high-dose inhaled glucocorticosteroid+LABA</td><td>Oral glucocorticosteroid</td></tr>
<tr><td>Leukotriene modifier</td><td colspan="2">Medium- or high-dose inhaled glucocorticosteroid</td><td>Leukotriene modifier</td><td>Anti-IgE treatment</td></tr>
<tr><td>-</td><td colspan="2">Low-dose inhaled glucocorticosteroids +leukotriene modifier</td><td>-</td><td>-</td></tr>
<tr><td>-</td><td colspan="2">Low-dose inhaled glucocorticosteroid +sustained-release theophylline</td><td>-</td><td>-</td></tr>
</table>
<u>Management of exacerbations</u>

Repeated administration of rapid-acting inhaled β_2-agonists is the best method of achieving relief for mile to moderate exacerbations.
Systemic glucocorticosteroids should be considered if the patient does not immediately respond to rapid-acting inhaled β_2-agonists or if the episode is severe.

<u>Special Populations</u>

LABAs may also be used to prevent exercise-induced bronchospasm and because of a more rapid onset of action, formoterol is more suitable for symptom relief as well as symptom prevention over salmeterol.
Appropriately monitored use of theophylline, inhaled glucocorticosteroids, β_2-agonists, and leukotriene modifiers, specifically montelukast, are not associated with an increased incidence of fetal abnormalities.
Inhaled glucocorticosteroids have been shown to prevent exacerbations of asthma during pregnancy.
Acute exacerbations during pregnancy should be treated with nebulized rapid-acting β_2-agonists and oxygen. Systemic glucocorticosteroids should be instituted when necessary.

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<tr><td>Global Initiative for Chronic Obstructive Lung Disease (GOLD): Global Strategy for the Diagnosis,</td><td>
<u>Diagnosis</u>

A clinical diagnosis of COPD should be considered in any patient who has chronic cough, dyspnea, excess sputum production, or history of exposure to risk factors including smoking.
A diagnosis of COPD should be confirmed by spirometry.

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</table>

Clinical Guidelines	Recommendations
Management, and Prevention of Chronic Obstructive Pulmonary Disease (COPD) (2008)[9]	• COPD patients typically display a decrease in both Forced Expiratory Volume in one second (FEV_1) and FEV_1/ Forced Vital Capacity (FVC) ratio. • The presence of a post-bronchodilator $FEV_1/FVC<0.70$ and $FEV_1<80\%$ predicted confirms the presence of airflow limitation that is not fully reversible. • A detailed medical history should be obtained for all patients suspected of developing COPD. • Severity of COPD is based on the level of symptoms, the severity of the spirometric abnormality, and the presence of complications. • Bronchodilator reversibility testing should be performed to rule out the possibility of asthma. • Chest radiograph may be useful to rule out other diagnoses. • Arterial blood gas measurements should be performed in advanced COPD. • Screening for α_1-antitrypsin deficiency should be performed in patients of Caucasian decent who develop COPD at 45 years of age or younger. • Differential diagnoses should rule out asthma, congestive heart failure, bronchiectasis, tuberculosis, diffuse panbronchiolitis, and obliterative bronchiolitis. <u>Treatment</u> • Patients should be instructed to avoid the exacerbating exposure. This includes assisting the patient in smoking cessation attempts and counseling the patient on how to avoid pollutant exposures. • The management of COPD should be individualized to address symptoms and improve the patient's quality of life. • None of the medications for COPD have been shown to modify long-term decline in lung function. Treatment should be focused on reducing symptoms and complications. • Administer bronchodilator medications on an as needed or regular basis to prevent or reduce symptoms and exacerbations. • Principle bronchodilators include β_2-agonists, anticholinergics and theophylline used as monotherapy or in combination. • The use of long-acting bronchodilators is more effective and convenient than short-acting bronchodilators. • For single-dose, as needed use, there is no advantage in using levalbuterol over conventional nebulized bronchodilators. • Inhaled corticosteroids should be used in patients with an $FEV_1<50\%$ of the predicted value. • Chronic treatment with systemic corticosteroids should be avoided due to an unfavorable risk-benefit ratio. • COPD patients should receive an annual influenza vaccine. • The pneumococcal polysaccharide vaccine is recommended for COPD patients ≥65 years old or for patients <65 years old with an $FEV_1<40\%$ of the predicted value. • Exercise training programs should be implemented for all COPD patients. • Long-term administration of oxygen (>15 hours/day) increases survival in patients with chronic respiratory failure. <u>Management of Exacerbations</u> • The most common causes of an exacerbation are bronchial tree infections and air pollution. • Inhaled β_2-agonists, with or without anticholinergics, and systemic

Clinical Guidelines	Recommendations
	corticosteroids are effective treatments for exacerbations of COPD. • Patients experiencing COPD exacerbations with clinical signs of airway infection may benefit from antibiotic treatment.
National Institute for Clinical Excellence (NICE): **COPD: National Guideline on the Management of COPD in Adults in Primary and Secondary Care (2004)**[10]	Diagnosis • Diagnosis should be considered in patients >35 years of age who have a risk factor for the development of COPD. • The primary risk factor is smoking. • Spirometry is diagnostic of airflow obstruction. Airflow obstruction is defined as FEV_1<80% predicted and FEV_1/FVC<70%. Treatment • Smoking cessation should be encouraged for all patients with COPD. • Short-acting bronchodilators, as necessary, should be the initial empiric treatment for t he relief of breathlessness and exercise limitation. • Long-acting bronchodilators (beta$_2$ agonists and/or anticholinergics) should be given to patients who remain symptomatic even with short-acting bronchodilators, if two or more exacerbations occur per year. • Inhaled corticosteroids should be added to patients on long-acting bronchodilators to decrease the frequency of exacerbations in patients with an $FEV_1 \leq 50\%$ of the predicted value. • Oral corticosteroids should be reserved for those patients with advanced COPD. • Theophylline should only be used after a trial of long-acting and short-acting bronchodilators or if the patient is unable to take inhaled therapy. Plasma levels must be measured since there is a larger side effect burden with theophylline. • Pulmonary rehabilitation should be made available to patients. • Noninvasive ventilation should be used for patients with persistent hypercapnic respiratory failure. Management of Exacerbations • Patients with exacerbations should be evaluated for hospital admission. • Patients should receive a chest radiograph, have arterial blood gases monitored, have sputum cultured if it is purulent, and have blood cultures taken if pyrexial. • Oral corticosteroids should be used in all patients admitted to the hospital who do not have contraindications to therapy. The course of therapy should be no longer than 14 days. • Oxygen should be given to maintain oxygen saturation above 90%. • Patients should receive invasive and noninvasive ventilation as necessary. • Respiratory physiotherapy may be used to help remove sputum. • Before discharge, patients should be evaluated by spirometry. • Patients should be properly educated on their inhaler technique and the necessity of usage and should schedule a follow up appointment with a health care professional.

Conclusions

The combination respiratory β_2-agonists in this review are Food and Drug Administration (FDA) approved for the treatment of bronchospasm associated with chronic obstructive pulmonary disease (COPD). The products are a combination of albuterol, a short-acting respiratory β_2- agonist, and ipratropium, a short-acting respiratory anticholinergic agent. The combination product as well as its individual components is available generically in a nebulization dosage form. However the combination product as well as its

individual components is only available as branded agents in a meter dose inhaler (MDI) dosage form. Current national and international guidelines support the use of the individual components for the control of COPD, and more commonly recommend the addition of an anticholinergic agent in patients who remain symptomatic while on a short-acting respiratory β_2-agonist.[7-10] The combination albuterol/ipratropium is generally recommended for patients who have had an inadequate response to monotherapy bronchodilator treatment. Clinical studies have shown that the fixed-dose combination product(s) are more effective than monotherapy with either component.[11-15] However there are no published studies comparing the combination products to concurrent administration of the individual components.

Recommendations

In recognition of the well-established role of the combination β_2-adrenergic agonists (albuterol/ipratropium) in the treatment of chronic obstructive pulmonary disease (COPD) and cost considerations, no changes are recommended to the current approval criteria.

Duoneb nebulizer requires prior authorization with the following approval criteria:

- The patient has a documented intolerance to generic ipratropium/albuterol nebulizer.

Combivent® (ipratropium/albuterol) metered dose inhaler is preferred on the OVHA Preferred Drug List (PDL) and may be obtained without a prior authorization.

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